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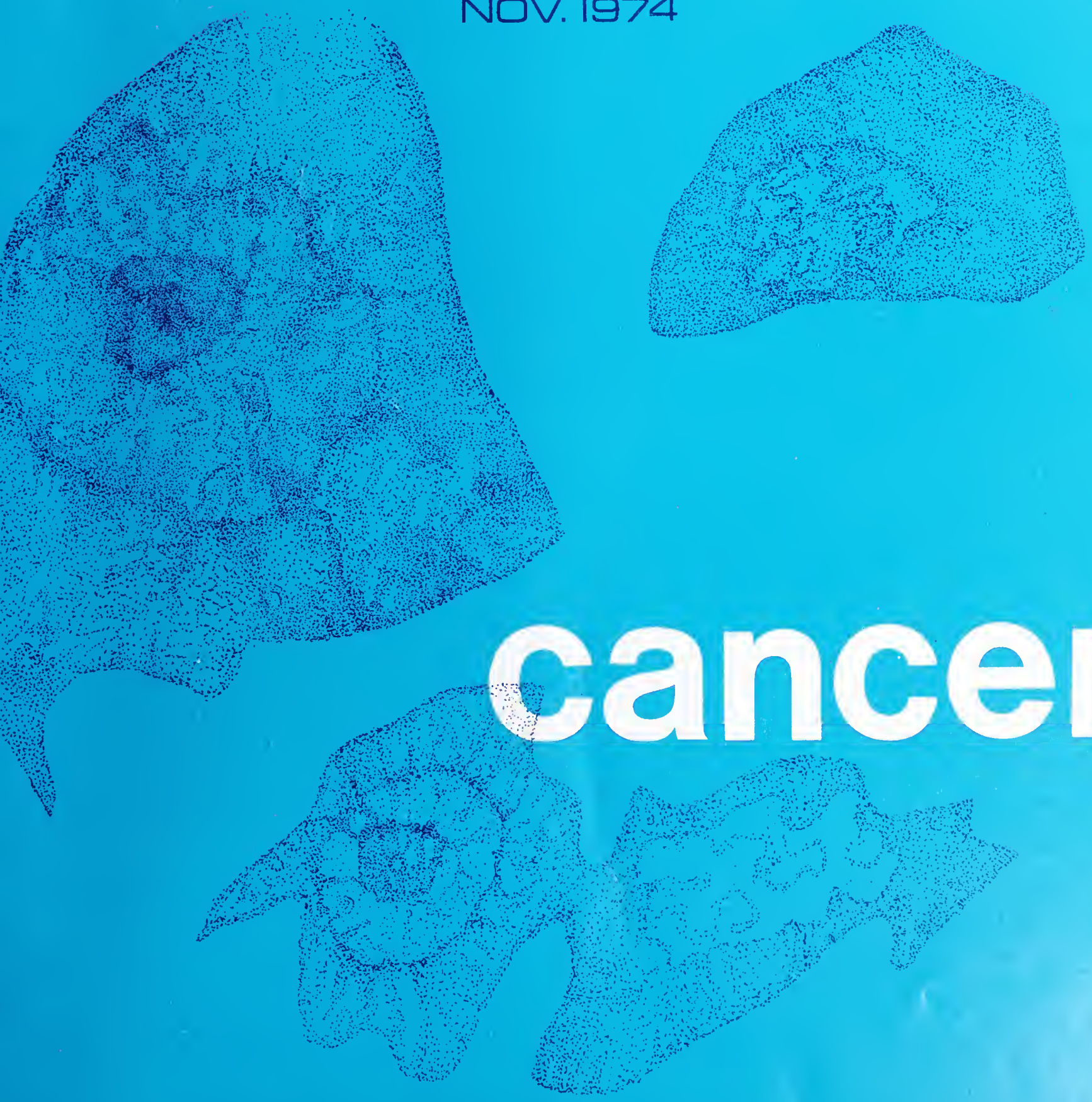

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Guest Editorial

ROBERT A. GOOD, M.D., Ph.D.
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The scientific revolution in medicine has been in progress approximately 100 years. In its ascendency it can be recognized, however, to be a youth of only about 30 years. For me this extraordinary revolution is attributable to a constructive interplay between a developing basic science and technology and the interpretation of "experiments of nature". Experiments of nature are chance conjunctions of natural events and uniquely prepared and concerned minds. Often the most useful experiments of nature derive from encounters at the bedside or in the clinic with patients who have unusual diseases. The problems of these patients can frequently be focused into unique questions that, taken to the laboratory, can be addressed by the developing technology, often in crucial model systems. This interaction yields answers that will be returned promptly to the clinic in the form of a medical advance and improved medical care.

The principles and concepts that derive from the the interaction between bedside and bench can often best be tested for relevance to man when they meet the challenge of another critical experiment of nature in the clinic. The unfinished revolution in medicine has yielded in 30 years a veritable conquest of bacterial infection and intoxication, the ability to prevent and even create herd immunity to many viruses like polio, measles and others, the ability to prevent erythroblastosis fetalis, safe blood transfusion and effective fluid and electrolyte therapy, elimination of rheumatic fever as a serious problem, effective treatment of nephroses of childhood, low risk open heart surgery, effective management of many endocrine problems, the ability to treat and prevent hypertensive cardiovascular disease and a beginning of understanding of etiologies and effective treatment of some cancers, especially those of children. These are only a few examples.

I believe implicitly that given proper backing, modern medical science assumes the extrapolation of this revolution of generally applicable treatments and preventions of all or almost all currently unresolved medical problems which we call disease. The impact of this most delightful of revolutions on the lives and ways of man must provoke our serious reflection for, given continued opportunities for conjoined clinical and fundamental investigation, the answers we seek will be with us before we are really ready.

Transfer Factor and the Reconstitution of Cell-mediated Immunity

D. K. Roberts, 7T8

At the present time, allergic responses are classified either as humoral or immediate-type, or as cell-mediated or delayed-type. Reactions belonging to the first group are mediated by free circulating antibodies, whereas those of the second group, as the names indicate, depend on specifically reactive or sensitized thymus-dependent lymphocytes ("T cells"), and evolve more slowly than humoral reactions. In responses of either variety, the first contact with the offending antigen is relatively mild, but has the important effect of sensitizing the individual – this means that he acquires specific immunologic memory of the antigen such that his immune system will mount a much more rapid and intense reaction in subsequent contacts with that antigen. Broadly speaking, immediate-type hypersensitivity reactions reach their peak in previously exposed individuals in a period of time ranging from several minutes to a few hours. Delayed-type reactions in immunologically experienced individuals do not reach their maximum intensity until at least one day has lapsed since exposure to the target antigen. Many clinical instances of allergic response are mixed, involving activation in an individual of antibody – and cell – mediated immune systems by a single antigen.

It has been observed of both types of response that hypersensitivity can be transferred from an experienced donor to an inexperienced recipient. Thus, one can induce the capacity for allergic response in naive individuals without exposing them directly to the antigen such that, when they eventually do encounter that antigen for the first time, it will provoke a secondary (intensified) reaction. For responses of the immediate type, this can be accomplished by transferring sensitized serum or "antiserum" (serum from an experienced donor). Delayed-type hypersensitivity can be conferred on a naive individual by introducing intact sensitized lymphocytes into him, as was first shown by Landsteiner and Chase[6] in guinea pigs; it has since been found that the T lymphocytes are the essential factor in transfer of this kind of hypersensitivity. Thus, using T cells from appropriately conditioned donors, one can transfer skin sensitivity, resistance to infectious agents, and transplantation immunity (characterized by an accelerated rejection of allografts over what would occur if the recipient were seeing the foreign tissue for the first time), all of which are examples of delayed-type hypersensitivity. While it is known that cell-mediated hypersensitivity cannot be transferred by antiserum (from which, by definition, lymphoid tissue is excluded), it has been shown by Lawrence[13, 14] that this type of hypersensitivity can be transferred by another cell-free solution, this one being an extract from sensitized lymphocytes. This paper is concerned with the active component of such extracts, which has been termed "transfer factor" (TF). Transfer factor has stimulated considerable research in the hope of obtaining new understanding about basic mechanisms of cellular immunity, and also of finding improved therapeutic methods to be used in dealing with certain intractable clinical conditions.

To date, TF has not been fully characterized chemically. As a result of work in the late 1950's and 1960's by Lawrence and others, which is reviewed in references [15, 16, 17], the following basic facts have been established about TF: it is of low molecular weight (less than 10,000); it is dialyzable; it is heat-labile (inactivated by 30 minutes' incubation at 56°C); it can be stored freeze-dried for years without losing its potency; it is not susceptible to treatment by trypsin, DNAase, or RNAase, nor by nucleases or lysomal hydrolases released by leukocyte lysis; it is not an immunoglobulin, and no antibodies have been found which inactivate it; it is, in fact, not immunogenic at all, and has never been observed to cause any kind of adverse immunologic reaction in vivo. Rosenfeld and Dressler[25] have recently reported that the active region of TF contains a short piece of double-stranded RNA, a finding confirmed by Burnet[5], who also cites unpublished results of Lawrence which indicate that the active region consists of 12 amino acid residues and 3 nucleotides.

There is equally little understood about the biological action of TF. There is much evidence which suggests that its effect is equivalent to sensitization by (transferred) educated T cells or to direct sensitization by the target antigen. In a normal individual, hypersensitivity acquired by any of these three routes is seen to exhibit three basic features: it is specific for the target antigen (more will be said about this below); it is systemic, meaning that contact with the antigen at any site in the sensitized individual's body will provoke a secondary response; and it is of prolonged duration (of the order of several months to a few years). That the recipient's immune system actively participates in the TF phenomena was shown by serial transfer experiments conducted by Lawrence – TF obtained from a natively sensitized donor was administered to a naive individual, who promptly acquired the donor's hypersensitivity; TF that was subsequently prepared from the recipient's lymphocytes was found to be capable of sensitizing another naive individual, thus demonstrating that the recipient's lymhocytes may be stably altered by injected TF.

Lawrence has found that TF arises in T lymphocytes; there is no known analogous substance in B cells. Through in vitro studies on naive lymphocytes cultured in the presence of both TF and its associated antigen, he has seen that TF initiates a process that duplicates what is observed when sensitized cells are cultured with their target antigen: transfer factor evidently converts nonsensitized T cells into an antigen-responsive state such that, when subsequently confronted with

the corresponding antigen, they undergo proliferation and blast transformation. He also noted that when sensitized lympyocytes are incubated with an appropriate antigen, they release TF into the cell-free supernatant solution. This suggests an identity between TF and other factors secreted by activated lymphocytes, which are collectively referred to as lymphokines. One of these, the so-called blastogenic factor (BF), is thought to induce sensitization, proliferation and differentiation into blast cells of naive lymphocytes cultured in the presence of some antigen[8]; BF apparently serves to recruit nonsensitized T cells, and its action in vitro depends only on the presence, not the nature, of the antigen. It seems that TF has an effect similar to that of BF, with the difference that TF will cause specific sensitization against a certain antigen even in the absence of that antigen – the proliferation and transformation stages follow naturally at a later time when the sensitized cells encounter their target antigen. Burnet[5] and Lawrence[16] are of the opinion that TF is a natural mediator of cellular immunity, and that it acts normally within an individual ". . . to recruit T lymphocytes to deal with situations such as delayed hypersensitivity or allograft rejection reactions for which there are inadequate numbers of immunologically reactive lymphocytes."[5] The phenomenon of hypersensitivity transfer between individuals was simply the first clinical manifestation of TF to be detected.

In order to determine whether TF confers de novo sensitivity on a naive recipient or whether it serves only to enhance an already existing but latent sensitivity in that individual, Lawrence et al conducted studies with coccidioidin as antigen. Coccidioides infection is restricted to the western United States, and the recipients selected were people who had always lived on the eastern seaboard, thus, who were unlikely to have ever been exposed to the antigen. TF prepared from donors who had previously had the infection was found to transfer delayed sensitivity to coccidioidin to these recipients, which persisted for over a year. This experiment constitutes sound evidence for the antigen-specificity of TF; however, this property is still not universally agreed upon. Dupont[7] reports unpublished results of work by Griscelli and collaborators in which acquisition of dinitrochlorobenzene (DNCB) sensitivity was noted in patients treated with TF obtained from DNCB-negative donors; Burnet[5] cites a similar example. However the majority of studies conducted on TF yield results in favor of specificity. Using the small chemical haptens DNCB and OCBC (ortho-chlorobenzoylchloride) as antigens (these would conjugate with native proteins within an animal and cause the proteins to appear alien), Rosenfeld and Dressler[25] prepared two batches of TF: #1, from guinea pigs sensitized only to DNCB, and #2, from guinea pigs sensitized only to OCBC. After administering TF #1 to naive guinea pigs and allowing 2 days for sensitization to occur, they found in all cases that, when challenged by both haptens, the test animals responded only to DNCB; the converse specificity was observed when the animals were treated with TF #2. Similar results were found by Levin et al[18, 27] who administered TF from normal donors to patients with Wiskott-Aldrich syndrome. This is a sex-linked immunodeficiency condition of which one symptom is negative response to all standard skin test antigens. In each case, the donor's allergy pattern over several skin tests was closely duplicated in the recipient (virtually no positive responses were noted for antigens to which the donor was not sensitive). Lawrence[17] has noted sharp specificity in the transfer by TF of the capacity for "second-set" (accelerated) rejection of homografts – TF prepared from an individual who has already rejected grafted tissue from a given donor will initiate second-set rejection in a recipient only of grafts from the same donor and not of unrelated grafts. The specificity of its T cell recruitment function could be accounted for by postulating that incorporated into TF is some portion of the target antigen which carries distinctive antigenic determinants. Considering the findings listed earlier on the size and chemical make-up of TF, it seems that TF is too small to be an informational macromolecule such as mRNA. Instead, one might hypothesize a regulatory role for TF, in which it exerts some influence such as derepression on gene expression in previously nonsensitized lymphocytes.

A feature of great clinical importance that has been observed in transfer of sensitized viable lymphocytes or of TF from a sensitized donor is that these practices may induce delayed-type hypersensitivity in recipients who have defective cell-mediated immunity. The benefit that can be obtained from therapeutic application of these methods depends on the extent and the nature of the impairment of the recipient's immune system. The two methods of transfer are being tested in a wide variety of clinical disorders in which the common denominator is some degree of failure in T cell responsiveness – this is often simply demonstrated by an anergic response to standard delayed hypersensitivity skin tests (the capacity to become sensitized to cutaneously injected antigens is depressed below normal, or is lacking entirely). The range in degree of immune deficiency is illustrated by Lawrence[61] with three diseases in man as examples; the first is largely a disorder of the antibody-mediated immune system, while the latter two affect primarily the cell-mediated system. Congenital agammaglobulinemia is characterized by drastically reduced serum immunoglobulin levels and by so-called immunologic amnesia – patients have the capacity to acquire delayed hypersensitivity responses under natural circumstances but have difficulty in sustaining the memory of this event. However, they respond to TF as do normal individuals, both with regard to the intensity and the duration of the transferred hypersensitivity. Patients with sarcoidosis do not have delayed-type skin reactions to any antigens, and they exhibit immunologic amnesia with respect to their response to administration of TF – they acquire sensitization but it is localized in the region of the injection rather than being systemically distributed; also it is transient and soon fades away. Patients with Hodgkin's disease, a generalized neoplasia of the reticuloendothelial system, are completely anergic and fail to reject skin allografts; as well, they show absolutely no response to TF of any specificity. There are many diseases in which the

deficiency is not so extreme and it is in such cases that early experiments with TF therapy are showing a certain proportion of successful results, not simply with regard to acquisition of hypersensitivity to standard skin test antigens but in the form of amelioration of the patient's condition. These include a variety of congenital or acquired immunodeficient syndromes, persistent disseminated infections associated with apparent paralysis of all thymus-dependent immune responses and different kinds of neoplasia. With diseases of the latter two groups, as will be explained below, it is believed that foreign cells go unchecked in the host, who is unable to mount an immunologic reaction against them – here the addition of TF from normal, immunocompetent donors serves to sensitize the host's T cells, or, as Dupont[7] puts it, to ". . . influence the immune response systems in such a manner as to bring to threshold level the potential for reactivity against so-called self-antigens."

In treating several conditions, transfer of sensitized viable lymphocytes is found to be just as effective as administration of an appropriate TF in reversing the patient's symptoms. This seems reasonable given Lawrence's claim that the educated lymphocytes will release TF once they encounter their target antigen within the diseased individual. However, the clinical use of intact sensitized lymphocytes in a naive host is limited by their immunogenicity; the recipient's immune system will recognize the histocompatibility antigens on the surface of the transferred lymphocytes as foreign, and a host-versus-graft reaction will ensue that will eventually destroy the cells. Thus, transfer of sensitized lymphoid tissue can mediate delayed-type hypersensitivity in the recipient for only a brief period of a few days, until the transferred cells are eradicated. The opposite situation arises in the event that the recipient is immunodeficient – if his T cells cannot actively maintain their allograft rejection function, then the foreign lymphocytes may survive and proliferate within the host; instead it will be the transplanted cells that recognize the host cells' histocompatibility antigens as foreign, leading to a graft-versus-host reaction against which the host cannot defend himself, and which is potentially fatal. In cases of the second variety, successful graft of sensitized lymphoid tissue should be possible if there is available a healthy donor who has a high degree of genetic identity with the recipient (e.g., a sibling) such that the two individuals' histocompatibility antigens are well-matched; in practice such a convenient solution seldom exists. In most circumstances administration of TF is clearly the superior method because it is nonimmunogenic.

Some of the most encouraging results of TF therapy have been obtained in treatment of patients with Wiskott-Aldrich syndrome, an X-linked disease that is usually fatal in childhood. These individuals are highly susceptible to a wide variety of infections; also there is marked abnormality in their cell-mediated immune system, as is demonstrated by their completely anergic response to skin antigens and by the defective in vitro blastogenesis of their lymphocytes in response to phytohemagglutinin (a plant protein that normally induces blast transformation). As one might expect, this is one instance in which there would be a great risk of a graft-versus-host reaction if transfer of intact lymphocytes were attempted. TF obtained from a normal donor was administered to a patient with the syndrome (reported in reference[18]) and he was subsequently observed to recover from his infections and to stay free of new disease. The investigators state that "the demonstrated changes are probably caused by improved host resistance resulting from induction of effective cellular immunity to the antigens to which the immunologically competent donor was resistant." Proof that cellular immunity had been transferred was seen in the fact that the patient acquired the donor's skin test pattern. It is interesting to note that the immunologic reconstitution achieved by such therapy was only partial – after treatment with TF from a DNCB-negative donor, the patient still responded negatively to DNCB and could not subsequently be sensitized to it; also the in vitro response of the patient's lymphocytes to phytohemagglutinin remained subnormal. Two years later, the same research group[27] published results of TF therapy in twelve patients with Wiskott-Aldrich syndrome. Clinical improvement was observed in seven of these cases, in all of which partial acquisition of the donor's skin test pattern occurred. Of note was the finding in two of the cases that relapse of the patient's condition could be reversed by further administration of TF – this cycle was repeated on several occasions and thus furnished substantial evidence that TF was mediating the cure. Ammann et al[1] have also published a study of TF therapy of six immunodeficient individuals, two of whom showed improvement to different degrees, and three of whom acquired some measure of delayed skin hypersensitivity from the donors.

A brief survey of the literature dealing with TF therapy applied to persistent intracellular infections did not turn up such positive results as those outlined above. There are isolated reports of recovery from generalized vaccinia and from disseminated coccidiomycosis (cited in [2] and [23] respectively.) Schulkind and collaborators [26] report that repeated injections of TF from a sensitized donor, combined with administration of amphotericin B, produced complete and stable recovery from infection in an individual suffering from chronic mucocutaneous candidiasis; the patient also acquired hypersensitivity to the antigens of the causative organism *Candida albicans*. These findings do not reflect entirely on the effect of TF because of the simultaneous use of amphotericin B. Another group [24] treated two of these patients with single doses of TF from donors sensitized to *C. albicans*, and noted that the only result was the transient acquisition by one patient (who was less severely afflicted to begin with) of delayed-type hypersensitivity to the *Candida* antigens. Similarly, single dose therapy with sensitized TF or whole lymphocytes of nine individuals with lepromatous leprosy, as conducted by Bullock and others[3], produced acquisition of a transient weak allergic response to *Mycobacterium leprae* antigens in some cases and no significant clinical changes. As an example of the diversity of conditions in which

TF is tested, two groups have reported giving TF from normal donors to patients with rheumatoid arthritis. Kass et al[11], who treated juvenile patients, observed substantial clinical improvement and augmentation of cell-mediated responses in all three of their cases, whereas Healey et al[10] found no improvement in adult patients.

The application of TF immunotherapy to cancer is based on two basic ideas about neoplasia for which there exists much experimental evidence. First is the notion that tumor cells have distinctive surface antigens that are lacking or are masked in the normal cells of the host; in general one should assume that these antigens are independent from the histocompatibility antigens which are also located on the cell surface. Because of these antigens, tumor cells should be immunogenic in the individual in whom the tumor arises, and should enable the host to react against the tumor as he would against an allograft. The second is the concept of a surveillance function of the delayed-type immune system (the system that mediates rejection of allografts). This was developed by Thomas and by Burnet[4], and it envisions the host's T cells recognizing (by their surface antigens) and destroying newly arisen neoplastic clones before they can achieve some critical size (above which the clones' rate of growth would exceed the rate of destruction caused by the immune response). Thus an individual in whom neoplasms have developed is regarded to be immunodeficient, and therapy is directed towards reconstituting his (cellular) immunity. One option is to inject cancer patients with TF from normal individuals, whose defense against neoplasia has evidently not lapsed and so TF should somehow be superior. However it is known that there exists a great diversity in the nature of tumor surface antigens and, given the antigen specificity of a TF preparation, one might expect a low likelihood of coincidence between the host tumor's surface antigens and the target antigen on the TF. The probability of a match could be increased by injecting TF that has been pooled from several donors who should, in the aggregate, have experienced a variety of tumor antigens. Alternatively, one could try to obtain TF that is specific for the most tumor antigens, by sensitizing lymphocytes against neoplastic cells removed from the host. In vivo sensitization, which implies introducing explants of the tumor into a donor, is clearly undesirable from the donor's point of view (in several of the studies listed below, this difficulty was removed by reciprocal transplantation of tumor grafts between two cancer patients, followed by reciprocal exchange of TF) and in vitro sensitization and subsequent extraction of TF is as yet not successful. Reciprocal sensitization between two cancer patients, in addition to being a desperate measure, is questionable in that cancer patients exhibit defective cellular immunity, as evidenced by decreased skin hypersensitivity, and so may not produce an active TF in response to the presence of foreign tumor cells.

Despite these problems there has been extensive research on TF immunotherapy of neoplasms, and some of the published results are cited here: several groups have treated patients with melanoma[9, 12, 21, 28], while others have dealt with osteogenic sarcoma[10], alveolar sarcoma[22], breast cancer[23] and nasopharyngeal carcinoma[9]. The number of patients studied is in most cases quite low, and also the criteria by which the benefits of the therapy were assessed seem to vary with the different studies. The range over these reports of the frequency of partial or complete remission is roughly 10% to 40%. Given the uncertainty of the effectiveness of TF, these are significant results, especially considering the occurrence in one study[21] of two complete remissions out of a total of 53 melanoma patients, and in another[12] of three complete remissions out of 56. In these large studies, the frequency of complete remission is seen to be roughly 5%, and it was also found that partial remissions could often be prolonged by repeated injections of TF. In many cases in which the disease was temporarily halted or even reversed, a concomitant improvement in the action of the cellular immune system was also noted – some in vitro reactions of the patients' lymphocytes approached normal behaviour, and there was increased lymphocytic infiltration of the tumors. These findings constitute definite evidence that TF therapy can enhance the immune system of patients with neoplastic disease. In none of these cancer studies, nor in the studies described earlier, was there a sign of significant adverse effect by TF.

It is clear that investigation into methods of sensitizing naive lymphocytes in vitro, especially against neoplastic cells, and of obtaining from them TF preparations, may afford valuable techniques to be used in immunotherapy of neoplastic disease. As was pointed out by Rosenfeld and Dressler[25], some of the current difficulties in the clinical use of TF stem from its variability and unreliability due to inadequate preparation methods. The fundamental mystery of TF is its chemical nature and the mechanism by which it confers sensitivity on naive T cells. Further research on the transfer factor will almost certainly yield new insights into cell-mediated immunity and new methods in clinical medicine.

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Warren Rubenstein, 715

". . . from the point of view of the greatest possible gain in early diagnosis, teaching women how to examine their own breasts is more important than teaching the technique of breast examination to physicians . . ."

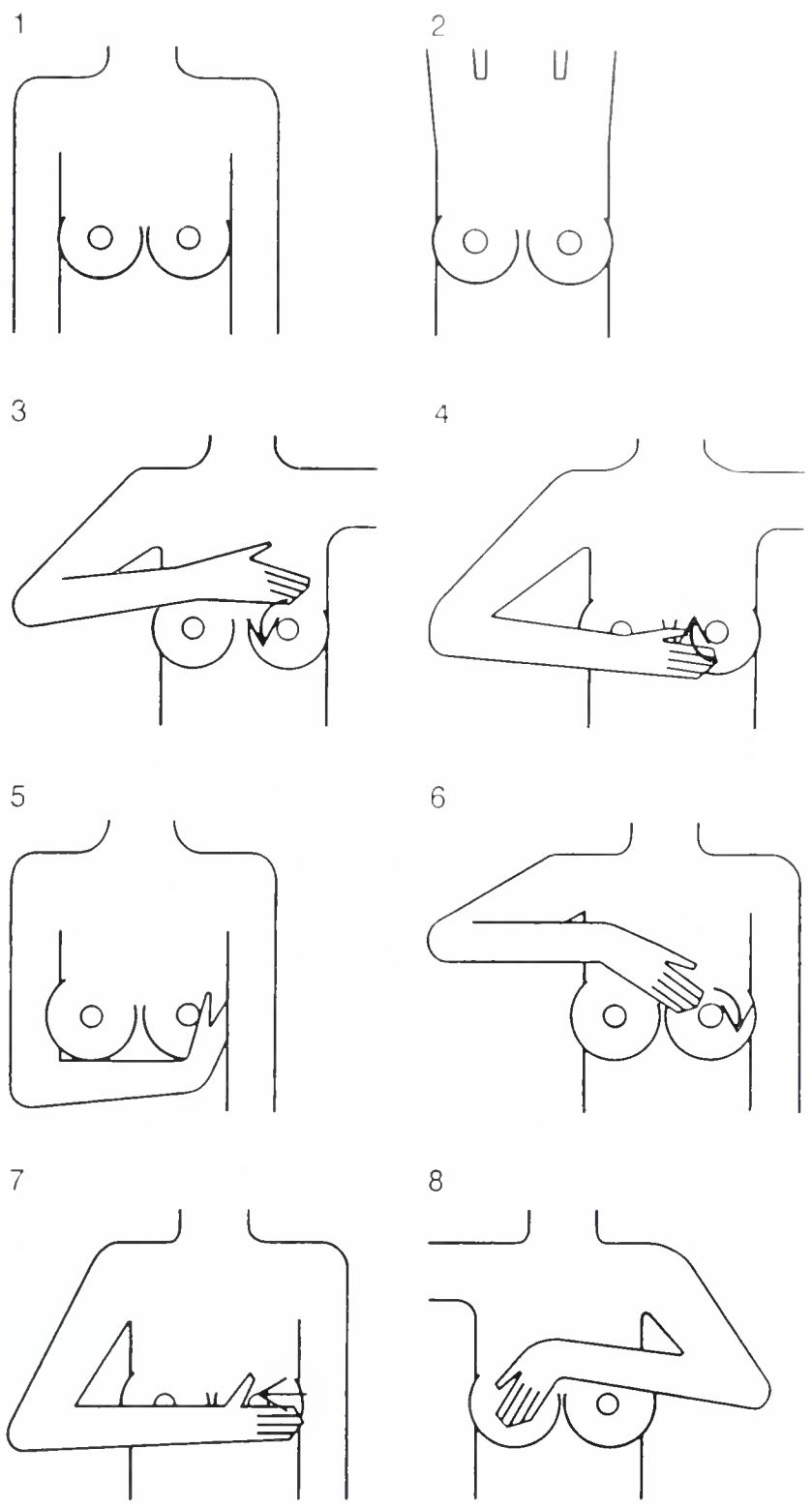
In 1958 a leader of the American Cancer Society espoused this theory with high hopes for early diagnosis of neoplastic breast disease. Over the years this premise was supported by the fact that published reports indicated over 90% of breast malignancies are discovered by the patients themselves[1, 2]. It was hoped that regular self-examination could detect these lesions earlier in the disease process, for it is known that Stage I disease (see table #1) has a much better prognosis. With radical mastectomy, 5-year survival rates as high as 70-80% are being claimed in Stage I breast carciomas[1, 3]. Stage II disease cuts survival in half.

Unfortunately, there have been very few controlled studies to determine the value of breast self-examination. In a recent complicated study, Thiessen[5] claims that only 39.1% of clinically confirmed lesions discovered by patients themselves were in women who claimed regular periodic breast self-examination and the rest were discovered apparently "by accident". With a few other such figures and some unexplained references to "biologic predeterminism",* he denounces the importance placed on self-examination. I fail to understand his thinking. All he has proven is that less than 2/5 of his patient population practise breast self-examination. He fails to show whether those lesions discovered by women practising self-examination were found at an earlier stage.

The value of self-examination has yet to be documented. But the theory would appear to be sound. The large majority of breast cancers present as lumps in the breast[6] (see table 2). They can generally be palpated when they reach about one centimetre in size. Thus, a woman who regularly practices self-examination and knows her breasts thoroughly will likely be able to discover a lump early in the disease process. Waiting for accidental discovery or for visible signs reduces the likelihood of finding highly treatable Stage I disease.

Over the last decade there has been only a minor effort to educate women about breast self-examination. This year the lay organizations have mounted a massive campaign. But another important mode of presentation has to be the physician's office – not by tossing pamphlets at the patients, but by taking a minute to explain this simple procedure to female patients, and even to their husbands. This policy has been adopted by the College of Family Physicians[7]. In a recent study only 35 percent of all women reported that a physician ever mentioned the topic of breast self-examination. Yet 92% of those who practised the technique had been personally taught by physicians[8].

Reprinted here is the technique as suggested by the Canadian Cancer Society. You, the physician, can play an important role in teaching and encouraging your patients.



BREAST SELF-EXAMINATION

1. Sit or stand in front of your mirror, with your arms relaxed at your sides, and examine your breasts carefully for any changes in size and shape. Look for any puckering or dimpling of the skin, and for any discharge or change in the nipples.

2. Raise both your arms over your head, and look for exactly the same things. See if there's been any change since you last examined your breasts.

3. Lie on your bed, put a pillow or a bath towel under your left shoulder and your left hand under your head. (From this Step through Step 8, you should feel for a lump or thickening.) With the fingers of your right hand held together flat, press gently but firmly with small circular motions to feel the inner, upper quarter of your left breast, starting at your breast-bone and going outward toward the nipple line. Also feel the area around the nipple.

4. With the same gentle pressure, feel the lower inner part of your breast. Incidentially, in this area you will feel

a ridge of firm tissue or flesh. Don't be alarmed. This is perfectly normal.

5. Now bring your left arm down to your side, and still using the flat part of your fingers, feel under your armpit.

6. Use the same gentle pressure to feel the upper, outer quarter of your breast from the nipple line to where your arm is resting.

7. And finally, feel the lower outer section of your breast, going from the outer part to the nipple.

8. Repeat the entire procedure on the right breast.

Your own doctor may want you to use a slightly different method of examination. Ask him to teach you that method. Examine your breasts every month, just after your period. Be sure to continue these checkups after your change of life. If you find a lump or thickening, leave it alone until you see your doctor. Don't be frightened. Most breast lumps or changes are not cancer, but only your doctor can tell.

TABLE #1*

Clinical Staging

Stage I	Early cancer confined to breast. No palpable axillary nodes
Stage II	Early cancer of the breast with palpable axillary nodes.
Stage III	Locally advanced cancer without palpable axillary nodes or small primary breast lesion with large palpable axillary nodes.
Stage IV	Breast cancer with distant metastases.

*Adapted from James [4]

TABLE #2

Presentation of Mammary Cancers[6]

(774 patients)

Painless lump	66%
Painful lump	11%
Nipple discharge	9%
Nipple crusting or retraction	5%
Local edema	4%

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* *Biologic predeterminism hypothesizes that, at the point of malignant transformation, the ability of the tumour to metastasize is established and is unrelated to early or follow-up treatment.*

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Possible Legal Implications of a "No Resuscitation" Order

Gale Rubenstein, Osgoode Hall '75

This year's Canadian Medical Association Convention, held June 23 to 28, saw the adoption of a resolution encouraging doctors to use the words "No Resuscitation" on the order sheet of a dying patient. The author of the resolution, Dr. E. Horniman of North Surrey, British Columbia, posited the view that the legal implications for the physician should not be decisive at that extreme stage of a patient's life and that ethical considerations should be paramount. However, the Convention adopted a further resolution referring the the decision to the Canadian Medical Association/ Canadian Bar Association joint committee[1].

While Dr. Horniman's concern for ethics and his patients are certainly laudable, I would suggest that it is not inappropriate for a physician who desires to continue his practice, to concern himself with the possible effects such a step might have on that practice in terms of a possible criminal charge, jail term or malpractice suit. A majority of doctors responding to a survey on euthanasia felt the law was of sufficient concern to warrant being examined and changed[2]. As a matter of fact, legal conduct and ethical conduct have been known to coincide. The law may at times be used to point the way toward the ethical things to do. This article will be a rather superficial look at the possible implications of a "No Resuscitation" order for the physician.

First, both criminal and civil law distinguish between acts and omissions, or, their equivalent terms, malfeasance and nonfeasance. Malfeasance refers to the performance of a wrongful act. Nonfeasance is the failure to perform, the omission, of a required act. A person may be criminally or civilly liable both for his acts and for his omissions. Thus a doctor who fails to administer a drug when one is required[3] and so causes death may be as legally responsible as one who administers the wrong drug and causes death. The resolution of the Canadian Medical Association calls for a positive action, the deliberate writing of words on a chart. Secondly, causation plays a major role in the determination of liability. Something the doctor has done or has failed to do must have caused, must have resulted in the death. Thirdly, the liability of nurses and assistants who follow doctors' orders depends on that of the doctor himself.

The distinction between acts and omissions for causation is of critical importance in the criminal area. According to Section 5.205 (1) of the Criminal code, a person commits a homicide when, directly or indirectly, by any means, he causes the death of a human being. However, homicide is only culpable, will only lead to prosecution, when death is caused (a) by means of an unlawful act or (b) by criminal negligence (5.205 (5)). Criminal negligence subsumes both acts and omissions and must involve "wanton or reckless disregard for the lives or safety of others".

As indicated, writing a "No Resuscitation" order on a sheet is a positive action, but one which in most cases will lead to no action, i.e., to omissions. Antibiotics will not be given if pneumonia sets in; oxygen will not be administered and cardiac massage will not be performed for arrest. Assuming that the physician's assessment is correct and the patient is indeed a terminal case, that there is no possibility of disputing that death was inevitable and foreseeable, then the physician, by his order, has not caused the death. His act of writing the order and the omissions that followed may have speeded the death or failed to delay it but they did not cause it.

The result is very different when a positive action is taken which directly results in death. For example, the wrong injection or an overdose given to a dying person will be culpable homicide whether done deliberately or negligently. The physician is just as responsible as a person who takes a gun and shoots someone slowly bleeding to death from an earlier stabbing, or for that matter, someone dying from cancer. The crucial point is the operative factor at the time of death.

The position is not clear when one considers the withdrawal of support systems already in operation, turning off or taking away blood, oxygen, and infusions. I would submit that the statements concerning omissions above would apply.

Civilly, the importance of the CMA's acceptance of the writing of the order as an ethical act, and its sanctioning as a recommended, acceptable practice for determining liability, cannot be underestimated. The level of competence or standard of care required of a physician by the law in any situation is based on the degree of skill one would expect from a medical person of ordinary ability. It sounds circular, and to some extent is. It means simply that the doctor is not expected to be perfect and is allowed mistakes and errors of judgment. He is expected to keep himself up-to-date on current practice, and to be as careful and as diligent as any ordinary physician would be. The level is established at trial by calling doctors as expert witnesses to testify as to what they would do and what is common and practical. One judge phrased it this way: "A doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men". Substitute "unethical conduct" for "negligence" and presume that the CMA is a "responsible body of medical men". The "No Resuscitation" order then becomes legally valid. Clearly, however, it is not quite so simple, and would not hold true where the doctor could be found guilty of homicide as indicated above.

The courts have to depend on the medical profession as the only source of information concerning technical medical problems. The same does not apply to questions of ethics. But, by and large, the judgment of the profession as a body will have a decisive impact on the judgement of the courts.

Further, litigation (court action) is initiated by a plaintiff who feels wronged and who may wish to see the defendant suffer. Ultimately, however, the function of litigation and the determination of liability is to to assess and order the payment of money damages. Specific expenses arising as a result of the defendant's acts are awarded, as well as the monetary value placed on attendant pain and suffering and loss of enjoyment of life. Punitive damages are rarely given. It is difficult to see how a judge could award any substantiated sum on any of these counts for the situations concerned here. Therefore civil liability is not, in all likelihood, a major problem.

I think it is important to reiterate that this is a very superficial treatment of a very complex subject. The preceding is based on the premise that the physician is accurate in forecasting an inevitable and essentially immediate death. I leave it to the doctors to judge their ability to do that.

FOOTNOTES

1. Special News Report – *CMA Journal,* Vol. 111, No. 1, P. 74.
2. Special Report – *Modern Medicine of Canada,* Vol. 29, No. 7, P. 659.
3. This would apply where the patient was not terminally ill in the sense that the proper drug would prevent death e.g. withholding insulin from a diabetic.
4. Other references:
    1. Smookler, K. M. – *Medical Post,* July 8, 1974.
    2. Sharpe, Gilbert – Medicine and the Law: The Standard of Care Required of a Medical Practitioner, *OMA Review,* Vol. 39, No. 3, 1972.

➡ **Keep for Handy Reference** ⬅

A Directory of Free Services to Your Cancer Patients

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codeine	methotrimeprazine	
dextropropoxyphene	morphine	

II. **Home Visiting and Activity Programme:** Carefully chosen volunteers visit the patient's home to provide comfort and recreation ideas.

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IV. **Homemaker Service**

V. **Home Nursing Service**

VI. **Transportation to Treatment Clinics**

VII. **Dressings** (prepared by volunteers)

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* Available from the Ontario Cancer Treatment and Research Foundation are:

1. Assistance with **therapeutic drugs**
2. Accommodation for patient requiring treatment at centres away from their home.

Preventive Medicine: A Different Perspective

Ann Matlow, 7T7
John Bohnen, 7T5

EDITOR'S NOTE: *This article was originally prepared for publication in the campus newspaper, "The Varsity". It is printed here to provoke some feelings, thoughts and action about preventive medicine in you, the physician. It can also be used as an approach to your patients when fielding questions about preventive medicine and cancer.*

The potential success of preventive medicine has been thrust almost entirely into the hands of the medical profession; the word "medicine" has never been completely divorced from those who prescribe it. As a result, prevention in terms of what the individual can do has been unjustly overlooked. Needless to say, health professionals do have the greatest responsibility as far as public health maintenance goes. The purpose of this article is not to condemn or condone their actions in this area. Instead, it is to focus on that aspect which has been neglected – the role of the individual in preventive medicine.

Each person has an indirect control over the basic body mechanisms. Although the body is provided with the means of transforming food to energy, the mind can often be held responsible for energy deficits and body malfunction. This occurs when the body's demands for external supplies are not met, or when it is left to deteriorate through disuse. The individual's role is to maintain a balance between what the body is equipped to do, and what the body does. When the balance is disrupted and equilibrium cannot be restored, the body is susceptible to a variety of signs of wear and tear. Therefore the goal is equilibrium. How can one help achieve it?

The body has various primary needs, and does not hesitate to make the mind aware of them. Some of the most obvious requirements are nutrition, sleep and exercise. It is often easy to neglect these needs, rationalizing in terms of a heavy schedule or pure laziness, while promising to be "better" in the future. This acceptance entirely overlooks the actual abuse that one is inflicting on one's physical framework.

And so, the body's needs: A short but necessary consideration.

NUTRITION: An inadequate diet is one of the more popular ways of mistreating the body. Many of those who can afford healthy food are poorly nourished. An intake of adequate amounts of protein, carbohydrate and fat is essential for proper body growth and function. Small quantities of vitamins and minerals are also necessary. Excessive intake is as detrimental as is undernourishment. If the body says it is hungry – feed it; if full, don't. When all the systems are functioning properly, the mind is as directly attuned to nutritional requirements as is the body. If programmed to attain maximal nourishment, it can guide the body to meeting this end, and in response to the activity of the body, it can direct or deter further intake. Such a feedback mechanism is nature's means of executing preventive medicine; the individual's role involves merely letting nature take its course.

REST: The principle of adequate rest is analogous to that of proper nutrition. Once again, the body is aware of its own sleep requirement. Although eight hours sleep has assumed the role of the classic quantity, it is by no means the necessary amount for everyone. Requirements vary in accord with demand. An excess use of energy in the course of a day might require compensation in a demand for additional sleep. If the body is unable to function well due to fatigue, its resistance to illness declines, and a state of physical and mental inadequacy prevails.

EXERCISE: The consequences of insufficient exercise can be even more harmful than those of lack of sleep. For both adequate heart and body functioning, physical exertion is essential. Working the heart enhances its ability to perform well. With the heart working efficiently to circulate oxygen, the other bodily functions work smoothly. Physical exercise affects other muscles, including those of the extremities and torso. By maintaining their flexibility and tone, muscle wasting, stiffness and other ill effects can be avoided.

So far, we have discussed preventive medicine directed towards maintaining a state of health. Practised lifelong, it will certainly make many diseases less likely to occur. If, however, disease does strike, "preventive medicine" takes on a different connotation – that of detection and correction. "Prevention" no longer applies to just a disease state, but to suffering, debility and death. As a particular example, let us focus our attention on cancer prevention.

How does one minimize the chances of being debilitated or killed by cancer? One must first have a basic knowledge of the disease process. Next, one should be aware of early signs and symptoms. If cancer is suspected, action must be taken to stop the progress of the disease. In this article it is not our intent to discuss the current state of cancer treatment; rather, we are concerned with preventive measures which can be taken by the individual.

"Cancer" has many meanings but basically refers to a group of cells which multiply too often and too fast. This can be in one small place, such as an area of skin, or all over the body as in leukemia, a cancer of blood. Some synonyms of "cancer" are "malignant tumour", "malignant neoplasm", and "malignancy". There are many different types of cancer, depending on the tissue of origin (e.g. carcinoma is cancer of epithelial tissue – skin, lung, intestine, and others). Two characteristics which distinguish cancerous tissue from other tissue in the body are: (1) its ability to invade and injure normal tissue, and, (2) the fact that cancer cells can leave the original tumour and form new colonies elsewhere in the body (metastasize).

Little can be said about the exact causes of cancer since the basic mechanism by which cells become

malignant is not known. Nevertheless, much is written about factors which seem to greatly increase the risk of cancer. Influences such as smoking, radiation and certain viruses are thought to act (usually in combination) to alter the genetic makeup of cells. The cells so altered do not function properly and forget to stop multiplying.

How does malignant tissue manifest its presence? This is of more than academic interest because it is the basis of the warning signs of cancer.

In very broad terms, malignant tumours disrupt the normal working of the body in two ways: metabolic (body chemistry) and mechanical. Usually the disruption is a combination of both. An example of a metabolic effect is the over-abundance of calcium in the blood seen in some types of cancer. Sometimes a patient will feel "unwell" (e.g. weakness, fatigue) in an early stage of cancer, on the basis of a metabolic derangement alone. Mechanically, a tumour can cause damage by eroding through or compressing normal organs, such as blood vessels. The specific ways in which malignancies destroy the body depend on many factors and are too numerous to mention here.

The seriousness of a given case of cancer also depends on many factors: the severity may range from almost totally curable to invariably fatal. Some important determinants are the speed at which the tumour grows, its site, its tendency to form new colonies, its metabolic effects, its response to various treatments and its time of detection. This last point is crucial. Technology has reached a halfway point in cancer therapy: many types of tumour (such as cancer of the cervix and breast) if detected early can be cured with little disability. Those that go unnoticed for months or years are much more likely to be debilitating. The person himself is best able to detect the early changes caused by cancer. This returns us to the idea of preventive medicine by the individual. The Canadian Cancer Society puts out a pamphlet called *The Seven Steps to Health* containing things one should do and look for to prevent serious illness. They are:

1. have a regular medical and dental checkup
2. watch for any changes in your state of health
3. watch for formation of any new lumps
4. protect yourself from excessive sunlight
5. don't smoke
6. have a regular Pap test
7. do a monthly breast self-examination

Finally, be aware of cancer's seven common warning signals:

1. change in bowel or bladder habits
2. a sore that does not heal
3. unusual bleeding or discharge
4. thickening or lump in the breast or elsewhere
5. indigestion or difficulty in swallowing
6. obvious change in a wart or mole
7. nagging cough or hoarseness

Remember these seven signs. More importantly, be as aware of your own body as you are of others'! Body and mind spend a lifetime together – they should be on good terms with each other.

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Kids and Cancer

Marshall Korenblum, 7T5

A Consideration of the Psychiatric Impact of Malignancy on Children and their Families *(First of Two Parts)*

Terminal neoplastic disease in children can have many effects on the psyche of the patients, their parents, and their physicians. It is the purpose of this article to examine these effects, and to recommend a particular approach which doctors should take when confronted with the problem of the dying child.

THE CHILD

A child's reaction to chronic illness and/or impending death is highly age-dependent. Up to the age of 3, his concerns are actually those of separation anxiety. Fears that his mother will die arouse as much concern as his own death. It is a fear of being isolated without a protecting/nurturing person, and reflects the child's incompletion and lack of clear boundaries between himself and his mother. In the insecure child, it can become a serious problem, particularly if his mother has left him for a prolonged period in his second or third year[1]. From 3-5, the child is fearful of mutilation. He begins to mobilize himself, learns about the integration of his body, and is frightened of anything that threatens this. He considers illness and death to be due to something outside himself. And death at this age is most closely associated in his mind with sleep, e.g., night terrors. From 5-6, degrees of disease and death begin to be perceived. From 6-9, terminal sickness is seen as a "bogey man" who comes to take people away. "Good people" can counteract this by such magical manoeuvres as a kiss. The 9-10 year old conceptualizes mortality in more realistic terms. He can recognize that death is a permanent biological process. Finally the adolescent, although he may understand what is going on, has a tendency to fight and rebel against a chronic illness due to his need to assert his independence and protect his identity.

The diagnosis of cancer can be viewed as a gross stress on the personality of the child who is old enough to understand what the disease is. Weiss and Payson[2] have described 4 phases of gross stress reactions, which are attempts to defend or restitute the personality from disorganization in the face of unusual circumstances. These are:

1) *the anticipatory or threat phase,* which may persist for the duration of the person's life. This refers to a tolerable but sufficient amount of "worry-work", i.e. pre-occupation with the future and the threatening stress. A certain amount allows the individual to assess the threat (in this case, malignancy), and take inventory of all strengths and supports he can use to to meet it. Excessive denial or unawareness of the disease deprives the individual of moderate worry-work and can result in overwhelming shock during the (next) impact phase, followed by permanent psychological incapacity. Excessive awareness, on the other hand, may turn the anticipatory phase itself into a prolonged impact phase, which can result in progressive disorganization and maladaptation. Thus, a small percentage of people become phobic about possible threats to their health, and utilize magical constructs (e.g. superstitious rituals) or the defense mechanism of "undoing" (as in the "cancerophobic" patient) to protect themselves.

2) *the impact phase.* Here, the focus of attention is on the present, rather than the future, and the phase lasts as long as the stress is present. During it, variable degrees of personality disintegration may occur. About 75% of people react initially by being stunned and bewildered, upon hearing that they have cancer. 12% are "cool and collected", 12% show inappropriate responses, severe confusion, or loss of control of motor behaviour (e.g. aggression, stereotypic actions, or catalepsy), and an unknown percentage lose consciousness either through syncopal attacks or by undergoing complete dissociative amnesia. The "cool and collected" group engage themselves immediately in anticipatory behaviour and eventually keep busy by trying to help others in similar situations. It is felt that this purposeful activity permits adaptive capacity to reduce anxiety. The "stunned and bewildered" group also gradually behaves in an automatic manner, which tends to be conditioned by contemplated or practised reactions to stress that occurred during the anticipatory phase. (This is why Phase 1 is an essential preliminary to successful psychological adjustment to the stress.)

3) *the recoil phase.* During this period, emotional expression, self-awareness, immediate memory and behavioural controls all begin to return. Though there may still be compulsive seeking for dependency attachments, these are manifestations of re-integration of adaptive function which was impaired during Phase 2. These restitutions and personality reorganizations, and the supportive intervention by others are of critical importance to subsequent psychological events.

4) *the post-traumatic phase.* This is when the sense of self has been maximally reconstituted. The full awareness of the trauma is to some extent socialized by group or individual support received during Phase 3. Successful stress reactions during Phase 4 involve sharing of the emotionally charged experience with others. Frequently very intense group loyalties begin at this time. Unsuccessful post-traumatic reactions seem to be characterized by permanently altered and often unfavourable concepts of the self, the group, and the outer world. Consequences of these are chronic anxiety, depressive and fatigue states, recurrent catastrophic dreams (in which the trauma is painfully re-experienced), and guilt ("Others with cancer have died

in order for me to live." Or "I almost died; I should have died; I'm dead"). Such guilt may be dissipated in phobic elaboration; defensive ceremonials; ties; rigid obsessional constriction of interpersonal relationships (which may be interpreted as an unconscious obeisance to and propitiation of the dead in order to be allowed to remain alive); anger; and (occasionally explosive social) aggression, especially in adolescents.

The above-described phasic responses, which overlap, are seen most clearly in children of school age or beyond. Pre-schoolers tend to show similar but less clear-cut patterns. One cannot predict with certainty a specific reaction of any individual unless a great deal is known about the pre-morbid personality and immediate social situation, for in each phase there is not only interaction between the stress and adaptive capacities of the individual, but between the physiological, psychological, and familial spheres, the last including all the dynamics which contribute to a family equilibrium.

Prugh[3] describes children's reactions to chronic and/or subacute illness, such as cancer, in a somewhat different way, classifying them as follows:

A. *Direct.* Malaise, discomfort, and pain, which may produce listlessness, prostration, sleeping and eating disturbances, and irritability. Particularly prominent in younger children are restlessness, anorexia, insomnia, and nightmares.

Reactive

1) Regression. This stems partly from the effects of the illness on the child's ego, and partly from an adaptive "retreat" and "regrouping of forces" by falling back on earlier, more familiar modes of handling stress. This is seen most strikingly in older infants and preschoolers, e.g. reappearance of thumbsucking, return to the bottle, more clinging, transient inability to talk, walk, or control bladder and bowels.

2) Depression. This arises from associated restriction or discouragement of activity, as well as separation from parents due to hospitalization. E.g., eating and sleeping disturbances, changes in motor behaviour, wide mood swings, feelings of helplessness, and hypochondriacal concerns.

3) Misinterpretation. This is related to the child's limited capacity for intellectual understanding and reality-testing, and his tendency toward magical or animistic thinking. E.g., pain from illness is punishment for wrongdoing.

4) Physiological concomitants of anxiety. These are due to psychological conflicts about the meaning of the illness, and may compound the effects of the physical illness, e.g., tachycardia, palpitation, hyperventilation, diarrhea.

5) Conversion reaction, especially in adolescents, affect voluntary skeletal muscles and somatosensory apparatus. This is an unconscious symbolic expression of emotional conflict. Many resolve in days or weeks. E.g., pain, vomiting, headache (incorporation of the physical symptoms into the conversion syndrome), dysphonia, weakness, easy fatigability, syncope, gait disturbances.

6) Dissociative reactions. These may compound or be compounded by actual delirium. Dissociative reactions arise in response to drug therapy, or may accompany widespread metastatic disease, with marked fever, e.g., amnesia, pseudo-delirium.

7) Perceptual-motor lags. Such lags may persist for weeks or months without apparent damage to the C.N.S., or may have resulted from temporary disturbance in cerebral metabolism (e.g. delirium in toxic state), e.g., chronic learning disability.

B. Effects on Personality. These range from overdependence, overanxiety, and passivity-withdrawal, with strong secondary gains from illness; to realistic dependence and acceptance of limitations with adequate compensatory outlets and no more denial than is consistent with the maintenance of hope; to overindependence and aggressiveness with strong tendencies to denial.

C. Effects on Body Image. These effects are most prominent in adolescents and are otherwise not that significant (except in very severe, far-advanced cases).

D. Reactions to Treatment

1) Paradoxical Response. In a small percentage of children, chemotherapy or surgery may be followed by psychological decompensation, conversion and other symptomatic reactions.

2) Family Pathology. In an unhealthy situation where the child's role as an invalid has become central, the precipitation of a remission may upset the tenuous equilibrium of adaptive forces, making it difficult for the child to assume a health role.

3) Steroid-Induced Psychosis. Particularly in adolescents, psychotic reactions occasionally develop in response to ACTH or cortisone, if these are part of the therapeutic regimen.

Finally, Dr. E. Kubler-Ross[4] has described 5 stages of typical emotional reactions to chronic illness and death. These stages represent a progression through a fixed order which may become "stuck" at any point if additional stresses are superimposed. They are, thus, a series of adjustments.

I. *Shock and Denial.* "No, it's not true".
This allows time for mobilization of other defenses.

II. *Anger and Protest.* "Why me?" Via projection the patient experiences relationships as attacks from the outside. The result is hostility and rejection.

III. *Bargaining.* "I'll make a deal with you." The angry child may remember that if he's good, he'll be rewarded. Maybe mother will take him home from the hospital.

IV. *Depression.* "It is sad to deal with the inevitable." When the bargaining is unsuccessful, two types of

depression take over, one concerning losses of the past, the other concerning losses of the future.

V. *Acceptance.* This is an adaptation to defeat and is, of necessity, the final stage.

In summary, stress is relative, not absolute. The individual's genetic endowment, his constitutional characteristics, his developmental capacities, and the nature of his past experience, including experience with the disease – all contribute to his adaptive capacity. This capacity, the nature, duration and intensity of the disease, and the current circumstances determine the degree of stressful significance and adaptive outcome.

Whether a child's illness produces a deleterious effect on his own or his family's equilibrium depends on:

1. the developmental level of the child
2. the child's previous adaptive capacity
3. the prior nature of the parent-child relationship
4. the existing family equilibrium
5. the nature of the illness including the organ system affected, the degree of prostration or pain, the type of treatment or home care, and any residual defect or handicap before the ultimate termination.
6. the meaning of the illness to the child and his family in terms of antecedent events and their actual or fantasized connection, the previous experience with such illness, the effect on the child's social, academic, and athletic capabilities, and the reverberations on the siblings.

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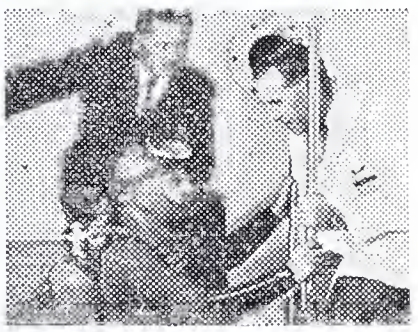

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DRS-70-21

Malignant Lymphomas - Report of a case and review of the Current Literature

Maurice N. Druck, 7T5

CASE REPORT

F.M. is a 14 year old Italian boy who was in good health until about 14 days prior to admission when he started to complain of pain in the back. The pain was at both costovertebral angles, more marked on the left side. It was dull but not radiating. He had no hematuria; however, he experienced occasional burning on micturition and three days later he developed fever. The fever was moderate to high, intermittent, higher at night, and was sometimes accompanied by chills and sweating. The fever persisted until admission to hospital. The patient was seen by his family doctor 12 days ago and was given Enterophen 10 gr. tabs t.i.d. for pain but this had no effect on the fever. As a result, he was put on tetracycline 250 mg. q. 6 h. for four days. This still did not affect the temperature. His family doctor also ordered a chest x-ray and an IVP, and according to his report these were negative. WBC was 3500, sedimentation rate 46 mm/hr, hemoglobin 13.6 gm/100 ml, urine clear. Specimens for VDRL and tuberculosis were sent to the provincial laboratory by the family doctor. There was no history of exposure to any infectious disease.

On functional enquiry there was anorexia, occasional nausea, and weight loss of about 4 lbs. during the last 14 days. There was no history of cough, shortness of breath, chest pain, joint pain or skin rashes, and no jaundice. Past medical history was not remarkable. He was born following a full term pregnancy and normal delivery. Birth weight was 10 lbs. He was fully immunized and had measles and chicken pox in the past. Family history was non-contributory.

Physical examination revealed a well nourished, well built but ill-appearing boy in no acute distress, slightly pale but not jaundiced. There was no edema, skin rash or lymphadenopathy. Examination of the ears, nose and throat was grossly normal. The pulse rate was 108/min, respiratory rate 18/min, blood pressure 110/70, temperature 39.5°C, and weight 77 kg. The abdomen was not distended or tender. Liver, spleen and kidneys were not enlarged. No masses were found. Bowel sounds were present and normal. The trachea was central. The chest was clear. Heart examination was normal. There were no neurological deficits and no signs of meningeal irritation. The extremities and joints were normal.

Admission diagnosis: Fever of Unknown Origin.

Laboratory investigations: These were ordered on admission and revealed the following results:

Blood and midstream urine cultures were sterile. Stool culture grew normal flora. Bone marrow culture also showed no growth of bacteria. The CBC showed the following results: hemoglobin was 12.6 gm/100 ml, WBC 3300 with 4% monocytes, 25% lymphocytes, 69% neutrophils, and 2% bands. Platelets were normal, hematocrit was 49.6%. The sedimentation rate was 48 mm/hr, and steadily increased to 91 over two weeks. pH was 7.46, Na 138, K 4.4, Cl 104, total CO_2 21, BUN 10 mg %, random blood sugar 117 mg %. Uric acid was 7 mg/100 ml, creatinine 1.05 mg %, alkaline phosphatase 21 Bodansky U, total bilirubin 0.45 mg, SGOT 16 U, LDH 173 U. Serial urinalysis was negative. The screening tests for infectious mononucleosis and LE cells were also negative. Viral studies revealed no adenovirus or varicella antibodies, and a titre of 1:8 to influenza types A and B. Serologic tests for *Salmonella typhi* and *paratyphi* were negative on two occasions. Chest x-ray showed normal lungs, mediastinum and pleural spaces. There was questionable splenomegaly present. Dorsal lumbar spine showed no articular radiographic abnormality and there was no calcification along the urinary tract. Renal outlines were normal as well. Barium enema was negative; upper GI series was also negative. X-rays of the left hip showed no evidence of fracture dislocation. ECG was normal. Bone marrow showed the following results: granulocytes 52.5%, erythrocytes 37.5%, lymphocytes 9%, plasma cells 1%, M:E ratio of 1.5:1. Liver scan revealed gross hepatomegaly, and the spleen was also enlarged in the PA view. There were no focal defects. The suggestion was made that this case might represent a hematological disorder such as lymphoma.

Following this extensive investigation, diagnosis was no closer than before. The tentative diagnosis of possible collagen disease rather than that of lymphoma was entertained, because no peripheral lymph node involvement could be found, and liver and spleen could not be palpated. The patient was discharged home on 2.5 gm ASA per day. A diagnosis of Pyrexia of Unknown Origin was made. Following discharge, the patient continued to complain of intermittent pain. Two days prior to readmission he had severe left-sided pain, and pyuria on admission.

On examination, there was left-sided tenderness but no other abnormalities were apparent. Emergency IVP showed poor function on the left, and on delayed film there was filling of the renal pelvis down to the transverse process of L3. Here a denser concentration of dye was apparent, suggesting the possibility of a stone.

The patient was taken to the operating room and under general anesthesia the left ureter was catheterized. A retrograde ureterogram and pyelogram demonstrated some obstruction at L3 and a peculiar irregularity along the entire length of ureter which could not be filled. It was decided to explore the retroperitoneum. Through a subcostal incision, the kidney was found to be swollen and tense, producing a large mass in the

retroperitoneum. There was considerable thickening of the retroperitoneal fat. A firm sheet of fibro-fatty tissue completely enveloped the lower pole of the kidney, ureter and testicular artery. The ureter was shelled out and multiple biopsies of the retroperitoneal fat and lymph nodes were taken. The pathology report stated, "The appearance is that of a poorly differentiated lymphoma, affecting the retroperitoneal tissue, the lymph node and the wall of the ureter, which is consistent with reticulum cell sarcoma (diffuse histiocytic lymphoma)."

Treatment consisted of cyclophosphamide, vincristine, prednisone and procarbazine. The patient was discharged on prednisone. Two weeks later, he was readmitted with right flank pain and a left pleural effusion whieh was tapped. He was given a course of methotrexate and his prednisone was tapered off. Radiation therapy was given at Princess Margaret Hospital and he continued on vincristine and prednisone. He was finally discharged home and will be carefully followed in the coming months.

MALIGNANT LYMPHOMA

Malignant lymphomas are divided into two main groups: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The new histologic classification for Hodgkin's disease is shown in table 1. Lymphocyte predominance is proven to have the best 5-year survival (90%). Nodular sclerosis also has a favourable prognosis and a more localized presentation than mixed cellularity, according to studies by Keller, Kaplan, Lukes et al (1968) and J. S. Butler (1971). Nodular sclerosis, which constitutes more than half of HD, is found quite often in young women with localized disease in the neck and mediastinum. Occasionally, there is a tendeney for ehange towards more malignant patterns, e.g. from lymphocytie predominance to lymphoeytie depletion.

TABLE 1 — HISTOLOGIC CLASSIFICATION OF HODGKIN'S DISEASE (HD)

	% 5-yr.survival	Reed-Ste'nberg cells	Lymphocytes	Eos'nophils Plasma cells Necrons	% of total cases
Lymphocyte predom'nance	90	+	++ ++	0	5
Nodular sclerosis	70	+ to +++	+ to +++	+	50
M'xed cellularity	35	++ to+++	+	++	40
Lymphocyte deplet'on	35	++++	+	++++	5

HD is spread via several routes. Contiguous lymphatic spread is the foremost and characteristic mode of dissemination and is easily explained by a knowledge of normal lymphatic anatomy. In this way, cervical HD is associated with mediastinal involvement via bronchopulmonary nodes and parenchymal lymphatics. Hematogenous metastasis is the next most important mode of spread. This readily explains extension to bone, liver, spleen, etc. Although it is suggested that neoplastic cells circulate and spread the disease, a controversy still exists whether at time of diagnosis, dissemination to the spleen and para-aortic nodes is a result of such spread or not. It certainly seems likely that the spleen with its filtration function is involved hematogenously and subsequent extension is via efferent lymphatics (spleen has no afferent lymphatics) to celiac and para-aortic nodes. It is also possible that para-aortic nodes are directly involved via the bloodstream. This is more than merely of academic interest, since the decision whether to irradiate or give chemotherapy depends largely on whether abdominal spread is hematogenous or via contiguous spread. There is also concern regarding non-hematogenous systemic manifestation of HD such as fever, pruritus, seizures and night sweats. It has been postulated that these and other changes such as elevated alkaline phosphatase and splenomegaly *sine* lymphoma may result from the direct effects of the etiologic agent of HD.

The new histologic classification of non-Hodgkin's lymphoma (NHL) is presented in table 2. The main histological features of importance are the presence or absence of nodules, and the nature of the predominant cell type, i.e. well-differentiated vs. poorly-differentiated (undifferentiated) stem cell. Thus the nodular type lymphoma has a better prognosis than the lymphocytic, lymphoblastie and so on. Even within the nodular type, the nature of the predominant cell also affects survival, i.e. nodular lymphocytic has a better prognosis than nodular lymphoblastic, and so on. As with the HD lymphomas, NHL tends to progress toward a more malignant tumour.

TABLE 2 — HISTOLOGIC CLASSIFICATION NON-HODGKIN'S LYMPHOMA (NHL)

	% of NHL	% 5-yr. SURVIVAL	MEDIAN SURVIVAL
1. Nodular – Lymphocytic – Lymphoblastic – Mixed lymphocytic Reticulum cell – Reticulum cell	10	53	5.0
2. Lymphocytic	35	25	2.4
3. Lymphoblastic	20	3	0.6
4. Reticulum cell (Histiocytic)	20	11	1.1
5. Stem cell	15	14	1.1

DISTRIBUTION OF NHL

Most, if not all patients who have nodal disease which is thought to be localized at the time of diagnosis will have positive lymphangiography and will be shown to have retroperitoneal node involvement. However, NHL of extra-nodal origin is, in a high percentage of cases, localized to the initial site(s) of diagnosis (e.g. throat, thyroid, etc.). These extra-nodal NHL comprise a substantial number of patients and have a favourable prognosis.

Staging of HD & NHL – Based on Rye, New York Symposium on Hodgkin's Disease.

I – Disease is limited to a single lymph node group.

II – Two or more lymph node groups either above or below the diaphragm.

III – Disease is limited to lymph nodes both above and below the diaphragm.

VI – Disseminated disease in lymph nodes and non-lymphatic tissue.

For Hodgkin's disease only, the absence or presence of systemic manifestations such as fever, night sweats, or pruritus subdivides the stage into A or B. This is shown to be important with respect to treatment choice.

Both lymphangiography and laparotomy/splenectomy are used to help diagnose and stage HD and NHL. Roughly 30% of patients with stage I or II HD are advanced to stage III because of an abnormal lymphangiogram. Biopsy seems to confirm the x-ray diagnosis from 90-100% of the time. Unfortunately, however, a negative lymphangiogram does not assure future freedom from abdominal lymphoma. About 33% of patients whose lymphangiograms were negative, and para-aortic nodes were subsequently left untreated, later demonstrated abdominal lymphoma[5]. As mentioned before, almost 100% of patients with NHL who have clinically localized disease will have positive radiographic studies. Laparotomy has a two-fold purpose: (1) to substantiate findings in x-ray studies; (2) to establish abdominal disease where lymphangiography has been negative. Almost all patients with positive lymphangiograms have abdominal disease proven by laparotomy. Of those patients with negative x-ray studies in stage IA or IIA, 20% are found to have abdominal involvement; stage IB or IIB, 40%. In patients with large and palpable spleens, only 50% are found to contain lymphomas. Abnormal liver function tests have a high correlation with abdominal lymphoma, not necessarily hepatic.

Generally it can be stated with reasonable certainty that 20% of patients at laparotomy will be transferred from stage IA and IIA to II, and 40% from IB and IIB to stage III. Laparotomy has heightened accuracy in lymphangiographic interpretation, even though the use of both diagnostic measures appears redundant. Despite its usefulness, laparotomy still carries a considerable risk. The main justification for laparotomy is only if such an operation will ultimately determine the form of further therapy (for example, whether therapy will consist of irradiation, chemotherapy or both).

CHEMOTHERAPY OF THE LYMPHOMAS

In Hodgkin's Disease, the role of chemotherapy is well-defined. Unfortunately this is not the case for the non-Hodgkin's Lymphomas. This is mostly due to:

(1) different distributions of disease

(2) wide range of sensitivities to cytotoxic drugs

Hodgkin's Disease

Drugs which are used effectively in HD are shown in table 3. Alkylating agents, vinca alkaloids, procarbazine and steroids are considered first-line drugs in treatment. Second-line drugs are used if these prove ineffective. All the drugs except the steroids produce direct cytotoxic effects on the tumours. Corticosteroids mainly alleviate systemic symptoms of the disease and help control anemia. Drugs are used either as primary therapy for advanced disease or as an adjuvant to radiotherapy.

When radiotherapy is the primary treatment, chemotherapy is indicated in two situations: (1) where it is necessary to rapidly relieve pressure on major airways, spinal cord, superior vena cava, or other vital structures; (2) to shrink large masses so that the radiotherapist has a smaller field to work with, thus sparing more normal tissues. A single injection of nitrogen mustard I.V. will usually relieve pressure and reduce size acutely. One must be careful not to give too much chemotherapy in such cases, in order to avoid bone marrow suppression and eradication of disease in the abdomen which may further delay accurate staging and treatment. Adjuvant chemotherapy is also given following curative radiotherapy in order to eradicate small foci of disease not detected by the staging procedure. It is important that such combined treatment is carried out in centres with experience in cytotoxic chemotherapy, as it may be very dangerous to give myelosuppressive and immunosuppressive drugs to patients whose hemopoietic and immune systems have already been suppressed by radiation.

Radiotherapy is the prime treamtent for stages IA and IIA HD. Stages IIIB and IV are treated solely with drugs. In this centre, stages IB, IIB, IIIA are treated by a combination of drugs and x-irradiation.

TABLE 3 — DRUGS USED IN TREATMENT OF HODGKIN'S DISEASE

Alkylating Agents	Corticosteroids	Bleomycin
Mustine hydrochloride	Prednisone	Adriamycin
Chlorambucil	Prednisolone	VM26
Cyclophosphamide	Procarbazine	
Vinca Alkaloids	Nitrosoureas	
Vincristine	1, 3-6 bis (2-Chlorethyl)-1-nitrosomea (BCNU)	
Vinblastine	1-(2-Chlorethyl)-3-cyclohexyl-1-nitrosomea (CCNU)	

Combination Chemotherapy

The MOPP drug combination of nitrogen mustard, vincristine, procarbazine and prednisone (see table 4 for treatment schedule) has a complete remission rate of 81%. This was found in patients who had widely disseminated disease (stage IV), and has led to long term survival for many and "cure" for a few.

The principles of combination chemotherapy are: (1) drugs are chosen which have different actions and are effective as single agents also; (2) courses of treatment are given with intervals intervening when no

treatment is given. This "rest" enables the body tissues to recover from the toxic effects; (3) combinations decrease the chance of resistance to any single agent; (4) more effective in producing complete remissions.

A similar combination of drugs substituting vinblastine for vincristine and utilizing a lower dose of prednisone is also used (MVPP, see table 5). Complete remission rates of 77% have been obtained, and remission was not influenced by the histological classification of the disease, or presence of systemic symptoms such as pruritus, sweating, fever and weight loss.

The question of maintenance chemotherapy is still controversial. The risk of prolonged marrow suppression and immunosuppression must be weighed against the small increase in length of first remission. Side effects of the drugs include nausea and vomiting from the nitrogen mustard, severe tissue necrosis if nitrogen mustard, vincristine or vinblastine are allowed to leak outside the veins, peripheral neuropathy and alopecia with vincristine. The main advantage of vincristine over vinblastine is that it has a less depressant effect on the bone marrow even though both MOPP and MVPP exert their main effects on the bone marrow. Blood counts *must* be watched on days 0, 7 and 14 in each course of treatment. If anemia, leukopenia and/or thrombocytopenia occur, drug dosages can be accordingly adjusted.

If patients relapse or fail to respond to MOPP or MVPP chemotherapy, a second line of drugs may be useful. These include BCNU, CCNU (see table 3), bleomycin and adriamycin. Partial remission rates are a depressingly low 4-5%.

Non-Hodgkin's Lymphomas

Several factors influence the outcome of chemotherapy of the NHL, including histologic classification (see table 2) and age of onset of the disease. Survival time correlates strongly with histologic type, patients with nodular lymphomas surviving significantly longer than those with diffuse lympomas. Patients with diffuse lymphocytic or mixed lymphomas who were under forty at the age of onset had a worse prognosis than those over forty but older patients with modular and mixed lymphomas did more poorly than those under forty. Combined chemotherapy is again superior to single agents especially in lymphosarcoma and reticulum cell sarcoma. It has been shown that the CVP combination of cyclophosphamide, vincristine and prednisone is more effective in producing remissions in both diseases than cyclophosphamide alone, with the difference greatest for reticulum cell sarcoma. Complete remission rates of up to 57%, with 89% of these lasting for greater than one year, have been obtained by the National Cancer Institute study. The MOPP combination has also been found to be effective in those cases of reticulum cell sarcoma in conjunction with cyclophosphamide, vincristine, cytosine and methotrexate in cyclical regime. (See table 6 for results of chemotherapy of previously untreated NHL.)

Although some patients with stage I disease NHL can be "cured" by x-irradiation, all other stages are treated by combination chemotherapy. As with the HD lymphomas, the use of lymphangiography and bone marrow biopsy, along with laparotomy in selected cases, will help improve staging and diagnosis, and eventually, treatment.

TABLE 4 — MOPP TREATMENT REGIMEN

DRUG	DOSAGE
(1) Nitrogen mustard	6 mg/sq. m. i.v. daily on days 1 and 8
(2) Vincristine	1.4 mg/sq. m. i.v. daily on days 1 and 8
(3) Procarbazine	100 mg/sq. m. orally daily on days 1-14 inclusive
(4) Prednisone	40 mg/sq. m. orally daily on days 1-14 inclusive

Six courses are given, with a 2 week interval between the end of one course and the beginning of the next.

TABLE 5 — MVPP TREATMENT: FIRST SIX COURSES

DRUG	DOSAGE
(1) Nitrogen mustard	6 mg/sq. m. i.v. daily on days 1 and 8
(2) Vincristine	6 mg/sq. m. i.v. daily on days 1 and 8
(3) Procarbazine	100 mg/sq. m. orally on days 1-14 inclusive
(4) Prednisone	40 mg. orally on days 1-14 inclusive

4 week gap between courses

SUGGESTED MAINTENANCE AFTER SIX COURSES

(1) Four courses of MVPP at 3 month intervals
(2) Three courses of MVPP at 4 month intervals
(3) Three courses of MVPP at 6 month intervals

TABLE 6 — RESULTS OF CHEMOTHERAPY FOR PREVIOUSLY UNTREATED NHL

Drug Combination	% complete remission	Duration of Remission (Months)
(1) MOPP	53% (Lymphosarcoma) 38% (R.C. Sarcoma)	11.7 (mean) 32.0 (mean)
(2) Cyclophosphamide Vincristine Prednisone 6-MP Procarbazine	100% (Lymphosarcoma)	7.0 (median)
(3) Cyclophosphamide Vincristine Cystosine arabinoside Methotrexate	60% (R.C. Sarcoma)	10.0 (median)
(4) Cyclophosphamide Vincristine Prednisone	57% (Lymphosarcoma)	79% survival at 1 year

RADIATION THERAPY

Hodgkin's Disease

Radiation therapy effectively obliterates localized HD. Local recurrence varies inversely with size of the dose (4% recurrence after 3½ to 4 week treatment of 3500-4000 rads). Let us first consider stages IA and IIA. Five and ten year survival rates reach as high as 84% and 68% respectively with high radiation dosage (greater than 2500 rads). No additional improvement has been found by extending radiation to include adjacent uninvolved lymph nodes. A study by the National Cancer Institute found a 5-year survival of 98% in stages IA and IIA after total nodal irradiation. It was thus established that such treatment will in fact prevent spread of HD below the diaphragm. However, the question still remains whether the total course of the disease is changed or whether detection of recurrence is merely masked.

Figures for stage IIB are 30% five-year and 13% ten-year survival. The stage III patient does poorly after total nodal irradiation (17% five-year). Laparotomy and splenectomy are usually undertaken first to define the extent of abdominal disease. Hepatic spread is so common in patients with splenic lymphoma that adjuvant chemotherapy is usually given. In this centre, combination chemotherapy is the primary treatment of stage III and irradiation is used as an adjuvant.

Non-Hodgkin's Lymphomas

Whereas in HD the role of radiation therapy is clear cut, NHL poses several problems: (1) The disease has a long natural history; (2) There is a high incidence of disseminated occult disease; (3) There is difficulty in categorizing the disease histologically; (4) Multifocal origin of the disease is possible. The NHL have a wide range of sensitivities to x-irradiation, ranging from extremely radio-sensitive tumours to those which are extremely radio-resistant. Since NHL often present as localized extra-nodal disease, NHL should be widely and aggressively irradiated. Many North American clinics use total nodal irradiation for stage III nodular lymphoma but there is no evidence that such treatment will improve the already good survival rate since the questions concerning patterns of spread of NHL have yet to be answered. Further studies in disseminated non-nodular NHL, especially the lymphoblastic lymphomas and the reticulum cell sarcomas, have shown that radiation therapy does not prolong 5-year survival.

In summary, the radiotherapeutic management of NHL requires individualization with respect to patient, extent of disease, sites involved and histologic type. A logical approach to the problem of widespread disease would be to use both irradiation and chemotherapy in order to hit both the bulky tumours and the small foci of cells.

It must be remembered, however, that radiation in the range of 4000 rads delivered to large fields may be accompanied by serious complications. In cases of chest irradiation, 5% of patients develop severe pneumonitis and/or pericarditis. Five to ten percent with neck irradiation develop radiation-induced hypothyroidism. Surprisingly, the bone marrow tolerates total nodal irradiation extremely well.

Much research is being carried out to try to improve methods of diagnosis and treatment. As a result, accuracy of diagnosis is improving, and 5 and 10-year survival rates are increasing for both HD and NHL. In some cases, there is even talk of "cure".

CURRENT ARTICLES ON WHICH REVIEW IS BASED

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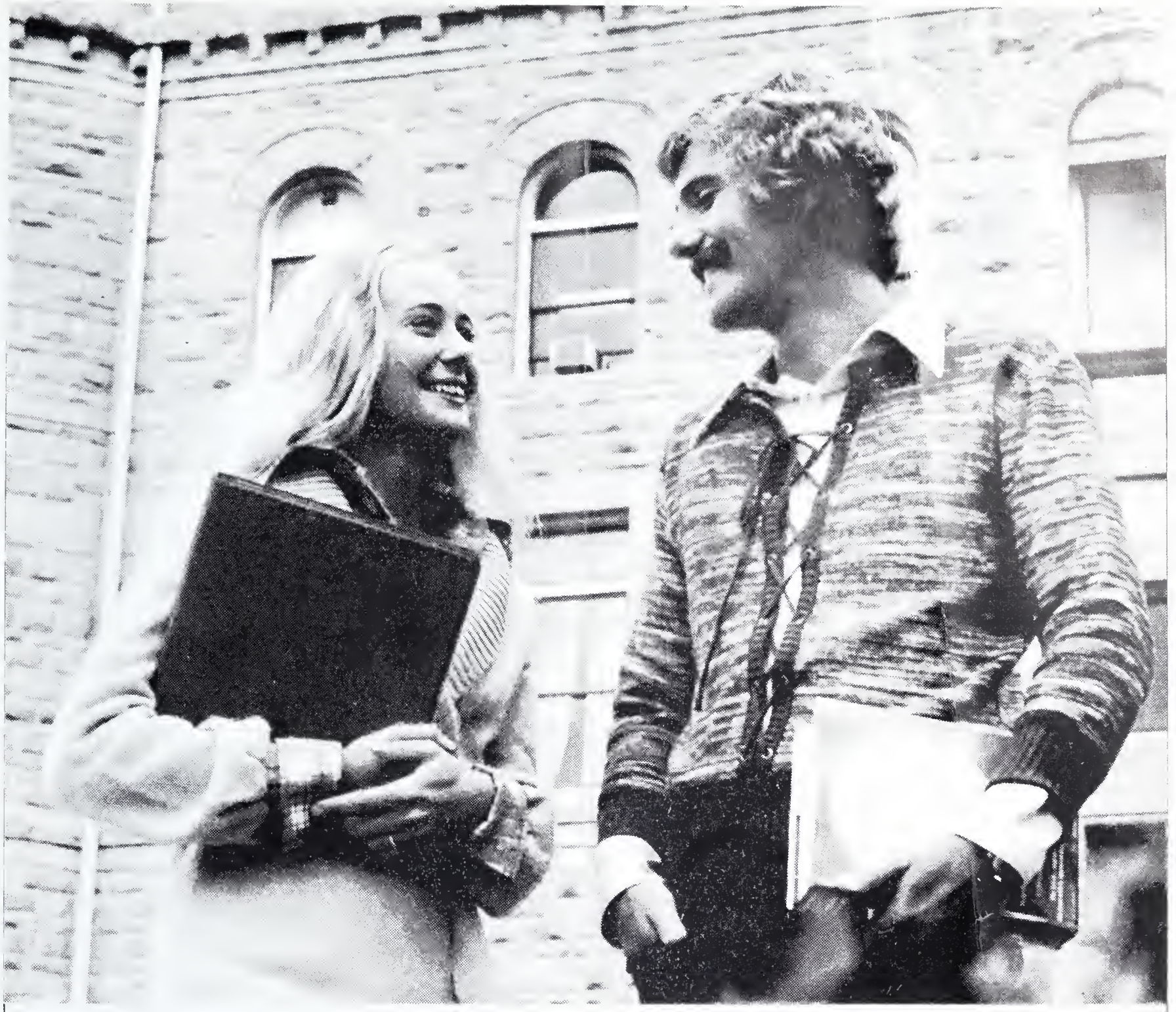

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the AOSC life insurance plan

You have invested a great deal in your education, and no doubt the expense will be justified when you graduate. But throughout your years at University you will encounter financial limitations, and more often than not, the net result will be a financial setback.

For this reason, the A.O.S.C. COLLEGE plan was designed and created **exclusively** for the University student. Its purpose is to provide you with the opportunity to insure yourself at a time when you need it, but can least afford it. Its coverage will provide you with the basis for financial security to protect you NOW.

TWOFOLD APPROACH

The A.O.S.C. COLLEGE plan approaches the student's position in a twofold manner. First, the plan provides term insurance at specially reduced rates, giving you the least expensive protection for an initial period of 5 years, with the option to renew for succeeding 5 year intervals. Then, it allows you to convert your policy at any time to permanent coverage suited to your particular need.

The low cost coverage thus ensures that you have some financial protection, but more importantly, begins your financial programme now, while you are young and insurable. The permanent coverage can then be obtained at a later date when your needs have increased and you are in a better position to develop your financial programme.

For Service Contact:

(A.O.S.C. COLLEGE PLAN)

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